Title

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Chapter 2

How to Identify Exposed Women Who Are Infected with *Neisseria gonorrhoeae*

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Abstract

Treatment trials of antibiotics for *Neisseria gonorrhoeae* infections frequently enroll primarily men with urethritis, as the diagnosis of acute gonococcal infection in men with urethritis is easily made by Gram stain of the urethral exudate, followed by confirmatory culture or nucleic acid amplification tests (NAATs). Enrolling women in treatment trials is of great importance, but *N. gonorrhoeae* cervical infections cause nonspecific symptoms. This makes it difficult to conduct interventional trials, as large numbers of women with nonspecific symptoms need to be screened for infection. Gram stain of cervical secretions has a strikingly low sensitivity, and culture and/or NAAT results are not available at the time of screening. This necessitates recall and delayed treatment of infected women who may not return and who may spread the infection during the interval. In this chapter we present an algorithm, derived from a comparison of women who did, or did not, become infected during exposure, which identifies those women who are highly likely to be infected before culture and/or NAAT results are available. The algorithm provides an efficient way to conduct interventional trials in women without the problem of recall and delayed treatment.

Key words *Neisseria gonorrhoeae*, Cervical infections, Cervical discharge, Vaginal pH, Cervical inflammation

1 Introduction

Treatment trials of antibiotics for *Neisseria gonorrhoeae* infections usually enroll primarily men with urethritis, as the diagnosis of acute gonococcal infection in men with urethritis is easily made by Gram stain of the urethral exudate, followed by confirmatory culture or nucleic acid amplification tests (NAATs) [1]. This allows enrollment during the initial clinic visit with subsequent censoring of the very few subjects whose infections will not be confirmed.

As *N. gonorrhoeae* acquires resistance to the currently recommended antimicrobials, enrolling women in treatment trials of newer agents is of great importance. However, *N. gonorrhoeae* cervical infections are asymptomatic in many women, cause nonspecific symptoms in others, and cannot be presumptively

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diagnosed with Gram stain of cervical secretions, as these have a strikingly low sensitivity (<0.1) [2]. This makes it difficult to conduct intervention trials. Asymptomatic women are unlikely to be screened, and large numbers of women with nonspecific symptoms will need to be screened for infection, but not enrolled until culture and/or NAAT results are available. This necessitates recall and delayed treatment of infected women who may not return to clinic and who may spread the infection during the interval.

One way to improve the efficiency of enrollment of infected women would be to recruit women who present to clinic reporting gonococcal exposure [1], but only 60–65% of women are infected with *N. gonorrhoeae* during a single exposure [3–5]. An algorithm that identifies women who are highly likely to have been infected during exposure, before culture and/or NAAT results are available, would allow for more efficient enrolment of women in interventional trials without the problem of recall and delayed treatment. We developed such an algorithm by comparing the medical and sexual histories, symptoms and physical findings of women who resisted infection during exposure with the same information from women who were infected during exposure.

1.1 Predictors of Cervical Infection During Exposure: Comparing Women Who Resisted Infection with Those Who Did Not

Here we present the development of the algorithm and how to use it to efficiently recruit women into treatment trials. The algorithm was developed by enrolling women who presented to one of the Baltimore City Health Department Sexually Transmitted Infection (STI) clinics with a "partner notification card" indicating sexual contact with a man who had been diagnosed with gonorrhea. We then compared sexual histories, symptoms and physical findings between those who were infected and those who resisted infection.

2 Materials

1. Subjects: women who have had sexual contact with an infected man.
2. A detailed history: a questionnaire that records sexual history—past prior STIs (including prior gonococcal infections), type of sexual contact involved (oral or anal sex in addition to vaginal intercourse), and the time between exposure and reporting to the clinic.
3. A cervicovaginal physical examination by a clinician experienced in the diagnosis of STIs.
4. Amsel criteria for bacterial vaginosis (BV) [6]: (a) A thin (i.e., of low viscosity) and homogeneous-appearing vaginal discharge. (b) Vaginal pH >4.5. (c) The release of a fishy amine odor on addition of 10% (v/v) potassium hydroxide (KOH) to a drop of vaginal discharge (whiff test). (d) Clue cells on saline wet mount of vaginal discharge.

Table 1
Cervicovaginal findings and risk of gonococcal infection during exposure

	Infected		Uninfected		
	N	% of all infected	*N*	% of all uninfected	p^a
Vaginal discharge observed by clinician	15	39.5	10	43.5	0.79
Cervical discharge observed by clinician	16	42.1	4	17.4	0.05
Inflammation (>5 WBC/hpf)	24	80	15	78.9	0.11
Positive "whiff" test	14	36.8	6	26.1	0.42

[a]Fisher's exact test

3 Methods

1. Recruit and enroll women who present to clinic having been identified as a partner of a man with acute gonococcal infection.
2. Record the presence of vaginal discharge on pelvic exam and whether it meets the Amsel criteria (*see* **Note 1**).
3. Measure vaginal pH by indicator strip (range: 4.0–7.0) (*see* **Note 2**).
4. Record the presence of cervical discharge on examination, and the presence of white blood cells (WBC) in cervical secretions (Table 1) (*see* **Note 3**).
5. Grade the degree of inflammation, as judged by the presence and number of leukocytes seen by the clinician on wet mount of the cervix (*see* **Note 4**).
6. Collect cervical swabs for gram stain (*see* **Note 5**), culture and NAATs (*see* **Note 6**), and wet mounts for KOH whiff test (*see* **Note 7**).
7. Scrutinize the sexual histories and symptoms recorded on the questionnaire (Table 2) (*see* **Note 8**) with particular attention to a history of oral sex and anal sex practices (*see* **Note 9**).
8. Calculate the interval between exposure and reporting to clinic (*see* **Note 10**).
9. Select female sexual contacts of men diagnosed with gonorrhea that presented within 30 days of sexual exposure and have a vaginal pH $\geq$5.0 but $\leq$6.5 for enrolment (*see* **Note 11**) and follow one of the two models in the algorithm (Fig. 1). The algorithm was constructed using the method detailed in **Note 12**.
10. Algorithm Model 1, which relies only on vaginal pH (Fig. 1—Model 1, Tables 3 and 4), enables enrolment of a larger number of infected women, but results in a lower percentage of

Table 2
Sexual history and symptoms and risk of gonococcal infection during exposure

	N	Infected		Uninfected		
All subjects	61	38	62.30%	23	37.70%	
History and symptoms		*N*	% of infected	*N*	% of uninfected	*p*[a]
Past gonococcal infection	25	15	39.5	10	42.5	0.79
Oral sex[b]	28	15	40.5	13	56.5	0.29
Mean days between contact and exam	61	24.3		25.76		
Median days between contact and exam		11 (0–120		8 (0–107)		
Any symptom	34	21	55.3	13	56.5	0.07
Vaginal discharge reported by subject	27	14	36.8	13	56.5	0.11
Abdominal pain	18	12	31.6	6	26.1	0.78
Regular douching	20	12	31.6	8	34.8	0.78
Hormonal contraception	15	8	21.1	7	30.4	0.54

[a]Fisher's exact test
[b]All reported vaginal intercourse, as well

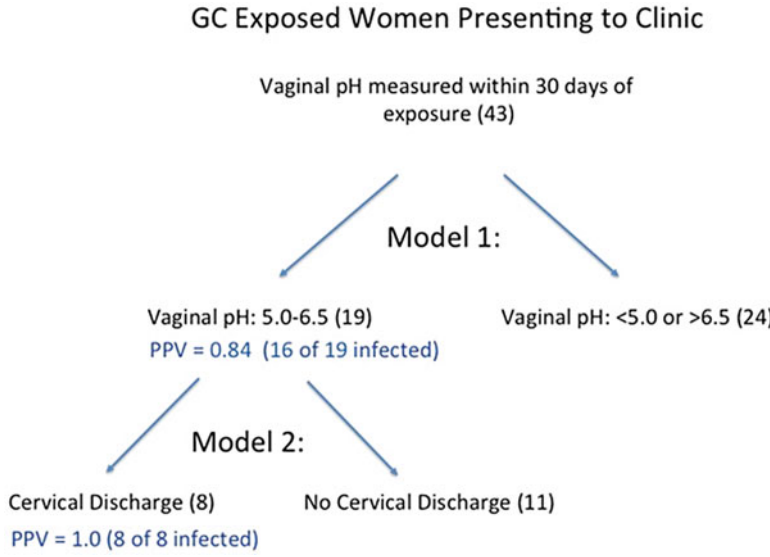

Fig. 1 Algorithm Models 1 and 2 begin selection by assessing vaginal pH of women exposed within 30 days of presentation to clinic. Model 2 continues by selecting women with a high likelihood of being infected by *Neisseria gonorrhoeae* during exposure based on vaginal pH and the presence or absence of cervical discharge

gonococcal-positive women enrolled. For example, if a study needs to enroll ~80 *N. gonorrhoeae* infected women, Model 1 could be used: 226 women who present reporting exposure to

a man with gonorrhea could be screened for vaginal pH, and the 100 women with a vaginal pH of 5.0–6.5 could be enrolled. This would result in around 84 positive women enrolled (16% uninfected women and 84% of infected women enrolled).

11. Alternately, if a study needs to enroll a small number of women, Model 2 could be used; Model 2 adds cervical discharge to vaginal pH (Fig. 1—Model 2). Fewer women will be enrolled, but virtually all of them will be infected. For example, if a study needs to enroll only ~16 infected women, Model 2 could be used: 86 women who presented reporting exposure to an infected man could be screened for both vaginal pH and cervical discharge sequentially; the 16 women with vaginal pH of 5.0–6.5 and cervical discharge would be enrolled, and this would result in 16 (100%) gonococcus-infected women being enrolled.

4 Notes

1. The BV discharge has a milk-like consistency and is distinctly not floccular, granular, curd-like, stringy, or clumped. Vaginal discharge of any sort was reported *more* frequently by uninfected women but was not always consistent with BV [7–9].
2. A vaginal pH >4.5 is one of the four Amsel criteria for bacterial vaginosis [6].
3. Only cervical discharge, but not vaginal discharge, was significantly more common among infected women than those who were uninfected ($p = 0.04$, Fisher's exact test).
4. Grade 4 inflammation was seen only in infected women ($N = 10$). Scale: 1 = 0–5 neutrophils/high-powered field (hpf; ×100 magnification), 2 = 6–30 neutrophils/hpf, 3 = 31–100 neutrophils/hpf, and 4 = >100 neutrophils/hpf.
5. Gram-negative diplococci were found in cervical secretions of only four women, including one uninfected woman. Sensitivity of gram stain in this study was only 0.079, but specificity was high (0.957).
6. Negative cultures will need to be confirmed by NAAT [1]. In our study, 38 of the 61 enrolled women were infected (62%), as determined by a positive culture (35) or a subsequent positive NAAT (3) after a negative culture.
7. A positive "whiff" test—the release of a fishy amine odor on addition of 10 % (v/v) KOH to a drop of fluid on a slide—is one of the four Amsel criteria for BV. Infected women were more likely to have a positive whiff test (37%) than uninfected

women (26%), but the difference was not significant (Table 1). Women who have BV by Amsel criteria should be treated.

8. Neither sexual practices nor a history of prior gonococcal infections nor any symptoms, including vaginal discharge and abdominal pain, differed between infected and uninfected exposed women (Table 2). It is unlikely that enrolling more women would reveal any significant differences. Note, in particular, that there was no difference in symptoms between infected and uninfected exposed women, so symptoms cannot be used to identify infected women. Platt et al. reported that infected women were more likely to have abnormal adnexal findings on exam [4], but abdominal pain was infrequently experienced by women in our study and did not discriminate between infected and uninfected women.
9. Oral sex is commonly acknowledged by exposed women (Table 2) and likely is more common than is acknowledged, as it may be considered part of normal foreplay. Questions of sexual practices need to be asked in the street vernacular. All women who acknowledge performing fellatio should provide pharyngeal cultures, as they may have pharyngeal, but not cervical infections. These same considerations apply to anal sex, asked in the street vernacular, and to anal cultures.
10. Because vaginal pH varies over time, the longer the interval, the less reliable is the pH as a marker of risk (Table 3).
11. Eighty-four percent of women who have a pH $\geq$5 and $\leq$6.5, measured within 30 days (~1 menstrual cycle) of exposure will be infected. Those who have a pH $\geq$5 and $\leq$6.5, measured within 5 days, will certainly be infected (Table 4).
12. Building the algorithm (generating a "predictive factors model"): STATA 14 statistical software used for logistical regression. Logistical regression was used to investigate the relationship between possible predictive factors (e.g., pH) and gonococcal infection and any relationship between a diagnosis of gonococcal infection and associated symptoms (e.g., cervical discharge) while accounting for possible confounders

Table 3
Risk as a function of vaginal pH range

pH range	*N*	Culture positive	Percent
4.0–4.9	23	11	47.8
5.0–5.7	13	11	84.6
5.8–6.5	16	11	68.8
>6.5	4	2	50

Table 4
Effect of interval between exposure and pH measurement

		pH 5.0–6.5		pH < 5		
Interval between exposure and measurement	***N***	***N***	**Infected**	***N***	**Infected**	***p*[a]**
All subjects	56	29	22 (76%)	23	11 (48%)	0.047
Within 30 days	43	19	16 (84%)	20	9 (45%)	0.019
Within 6 days	21	12	11 (92%)	9	4 (44%)	0.046
Within 5 days	17	9	9 (100%)	8	3 (38%)	0.009

[a]Fisher's exact test

(e.g., age). The "predictive factor model" was built using backward variable selection with variable inflation factor (vif) analysis to exclude possible collinear variables. Covariates included were taken from a detailed history of women presenting to clinic as gonococcal contacts with partner notification cards. This included age at sexual debut, the number of lifetime sexual partners, prior STIs, including gonococcal infections, the number of gonococcal infections, gonococcal infections in the past 6 months, whether the subject contact involved oral or anal sex in addition to vaginal intercourse, the time between exposure and reporting to the clinic, the date of last menstrual period (LMP) and the use, and type, of hormonal contraception if any. A history of regular douching was recorded, along with a history of vaginal discharge and its duration, and a history of abdominal pain. There was no difference in symptoms between infected and uninfected exposed women, so symptoms cannot be used to identify infected women (Table 2). Menstrual cycle phase, and bacterial vaginosis by Amsel Criteria [6] were excluded from the "predictive factors model" due to colinearity with pH.

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